II. REMARKS

Formal Matters

Claims 57-64 and 66-71 are pending after entry of the amendments set forth herein.

Claims 57-71 were examined and were rejected.

Claims 57-60 and 66 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. The amendments to claims 57-60 reflect suggestions made by the Examiner. Support for the amendments to claims 57-60 is also found at, inter alia, page 12, lines 13-19. Support for the amendment to claim 66 is found in the claims as originally filed, and throughout the specification, in particular at the following locations: page 10, lines 17-19. Accordingly, no new matter is added by these amendments.

Please replace claims 57-60 and 66 with the clean version provided above.

Claim 65 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Priority Claim

Applicants have noted the Examiner's position regarding the full scope of priority being afforded to the provisional application 60/089,146 filed on June 12, 1998.

Rejection under 35 U.S.C.§112, first paragraph

Claims 65 and 66 were rejected under 35 U.S.C.§112, first paragraph, as allegedly containing new matter.

Claim 65

The Office Action stated that the specification does not provide literal support for the recited ranges of polynucleotide to protamine sulfate.

Claim 65 is canceled without prejudice to renewal, thereby rendering this rejection moot.

Claim 66

The Office Action stated that the specification does not provide literal support for the use of dextran sulfate as a condensing agent.

Without conceding as to the correctness of this rejection, claim 66 is amended to recite "wherein the condensing agent is a polycation." Support for this amendment is found in the specification at, e.g., page 10, lines 17-19.

Applicants submit that the rejection of claims 65 and 66 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, second paragraph

Claims 57-71 were rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

Clams 57-71

The Office Action stated that the methods recite no step in which the aerosol is delivered. Applicants respectfully traverse the rejection. Claim 57 recites "**delivering an aerosol** to a patient while adjusting both particle size in the aerosol and volume inhaled." Thus, the methods recite delivery of an aerosol.

The Office Action stated that it is unclear what is meant by "free air volume."

Claim 57 is amended to recite "aerosol-free air." Support for this amendment is found throughout the specification, including, e.g., on page 12, lines 13-19.

The Office Action requested clarification of the phrase "aerosol volume is controlled along with free air volume inhaled prior to and following inhalation of aerosol."

Claim 57 is amended to recite "further wherein aerosol volume inhaled is controlled, and wherein aerosol-free air volume inhaled prior to and following inhalation of aerosol is controlled."

Claims 58-60

The Office Action stated that the term "particle size" lacks antecedent basis. Claims 57-60 are amended to recite "aerosol particle size," as suggested in the Office Action.

Applicants submit that the rejection of claims 57-71 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§103

Claims 57-62, 70 and 71 were rejected under 35 U.S.C.§103 as allegedly unpatentable over Debs (U.S. Patent No. 5,765,353; "Debs"), Crook ((1996) *Gene Therapy* 3:834-839; "Crook"), Schuster et al. (U.S. Patent No. 5,906,202; "Schuster"), and Radhakrisnan (U.S. Patent No. 5,049,389; "Radhakrisnan"). Claims 63-65 and 67-69 were rejected under 35 U.S.C.§103 as unpatentable over Debs, Crook, Schuster, and Radhakrisnan and further in view of Gao et al. (U.S. Patent No. 5,795,587; "Gao") and Curiel et al. (U.S. Patent No. 5,547,932; "Curiel").

Comments regarding instant invention as claimed

The instant invention as claimed relates to a method of targeted delivery of a polynucleotide to an area of a patient's respiratory tract. Three different factors come into play in targeting the area of the lung.

First, the formulation includes a **polynucleotide and a condensing agent**. The condensed polynucleotide makes is possible to form particles which are more easily aerosolized to create the desired size for inhalation and targeting. Further, by condensing the polynucleotide they are less susceptible to enzymatic degradation as disclosed at page 10, line 13.

Second, the **size of the aerosol particles is adjusted** so that the aerosol particles more readily fit in the area of the lung being targeted. The larger particles will not reach to the alveoli and the much smaller particles will pass through the upper and middle areas of the airway.

Third, the **volume inhaled is controlled**. First by controlling the amount of aerosol-free air inhaled prior to inhaling any aerosol, second by inhaling a predetermined volume of aerosolized

particles and third by inhaling additional aerosol-free air after the aerosol is inhaled (see an example at page 32, lines 10-24). These basic concepts claimed in claim 57 of (1) adjusting aerosol particle size and (2) inhaled volume of an aerosolized (3) formulation comprised of a polynucleotide and condensing agent are not taught in the cited art as taken alone or in combination. Accordingly, reconsideration and withdrawal of the rejections is respectfully requested.

The cited art does not teach adjusting the size of the particles of aerosol within a given range in order to target an area of the lung while also adjusting the inhaled volume of aerosol along with the inhaled volume of free air prior to the aerosol inhalation and after aerosol inhalation in order to target a particular area of the lung. Still further, the art does not teach these concepts in combination with the use of a condensing agent with a polynucleotide in order to create very small particles which are more readily formed into the aerosolized particles and which further allows the polynucleotide to be resistant to degradation.

In deciding the question of obviousness under 35 U.S.C. §103 it is not realistic to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of the other parts necessary to the full appreciation of what such a reference fairly suggests to one of ordinary skill in the art. Here, the taking of the disclosure from Debs relating to inhaling nucleotides and combining such with Schuster which discloses adjusting the particle size is not realistic in that Debs is not teaching towards the adjustment of inhaled volume in order to target areas of the lungs. Indeed, Debs cannot have taught toward adjustment of inhaled volume, since Debs only discloses use of a nebulizer, and use of a nebulizer does not allow control of inhaled volume. Thus, Debs does not provide any motivation to combine the cited references.

Radhakrisnan merely discusses lipid particle formulation for delivery of steroids into the lung. Radhakrisnan is not concerned with delivery of polynucleotides condensed into particle sizes of from about 20-50 nm, nor is there any disclosure of control of inhaled volume. Radhakrisnan provides no motivation to combine the above-discussed three features of instant claim 57. Gao merely mentions aerosol delivery of lipid/nucleic acid complexes, without addressing any of the issues discussed above, such as delivery to a specific region of the respiratory tract. Similarly, Curiel makes a passing mention of aerosol delivery of nucleic acid complexes, but does not address the issue of targeted delivery.

The mere existence in the cited art of individual features of a claimed invention does not, without more, render the claimed invention obviousness within the meaning of 35 U.S.C. §103. There must be positive evidence that the bringing together of such features or steps would have been obvious to an ordinary skilled person. Here there is **nothing to suggest that the bringing together of all of the claimed steps would result in a method making it possible to specifically target areas of a patient's respiratory tract with aerosolized particles of a polynucleotide which has been condensed with a condensing agent**. In view of such reconsideration and withdrawal of the rejections is respectfully requested.

Applicants submit that the rejection of the claims discussed above under 35 U.S.C. §103 has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AERX061.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Sept. 18, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the amendments to claims 57-60 and 66.

57. (Amended) A method of targeting an area of a patient's respiratory tract, comprising:

delivering an aerosol to a patient while adjusting both aerosol particle size in the aerosol and volume inhaled;

wherein aerosol particle size is adjusted to an aerodynamic diameter related to a diameter of a targeted area of the respiratory tract within a range selected from the group consisting of:

(a) 1-3 μm to target alveoli of the respiratory tract;

(b) 4-6 μm to target central airways of the respiratory tract; and

(c) 7-10 μm to target upper airways of the respiratory tract; and

further wherein aerosol volume inhaled is controlled, and wherein [along with free] aerosol-free air volume inhaled prior to and following inhalation of aerosol is controlled; and

still further wherein aerosol particles are comprised of a polynucleotide and a condensing agent which results in condensing polynucleotide particles to a size in a range of from about 20 to 50 nanometers, thereby delivering the particles of aerosol to a targeted area of the patient's respiratory tract.

58. (Amended) The method of claim 57, wherein the aerosol particle size is adjusted such that the aerodynamic diameter of the particles is in a range of from 1-3 μm.

59. (Amended) The method of claim 57, wherein the aerosol particle size is adjusted such that the aerodynamic diameter of the particles is in a range of from 4-6 μm.

60. (Amended) The method of claim 57, wherein the aerosol particle size is adjusted such that the aerodynamic diameter of the particles is in a range of from 7-10 μm.

66. (Amended) The method as claimed in claim 57, wherein the condensing agent is a polycation [dextransulfate].